THE TREATMENT OF SUBACUTE COMBINED DEGENERATION

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I AM reluctant to precede Dr. Carmichael in opening this discussion because the work I wish to describe is mainly of an experimental nature, and although it is difficult to avoid the conclusion that the results have some bearing on the ætiology and treatment of subacute combined degeneration of the cord, the evidence at present available is by no means conclusive. Indeed, the facts to be described may only add to the difficulty of the situation. However, there have been so many examples in recent years where experimental and clinical investigators have met together and discussed—with fruitful results—problems of disease, from what appear at first sight to be points of view with very little in common, that we can probably afford to be optimistic even on the present occasion.

Some essential points to be borne in mind in considering this disease are that it is a condition of nerve degeneration in the spinal cord and peripheral nerves, that the nerve changes are primarily those affecting the myelin sheaths, that the degenerative changes are unaccompanied by inflammatory reactions and with little or no neuroglial overgrowth, and that subacute combined degeneration is classed with pellagra, convulsive ergotism, and lathyrism, as toxic and not infective in character. If the spinal cord of a patient deceased of any of these diseases was presented to a pathologist for diagnosis, he would probably have some difficulty in deciding which was responsible for death.

A further point of fundamental importance is that all recent work has emphasized the fact that subacute combined degeneration of the cord is a metabolic disease. Its close association with pernicious anæmia—now controllable by liver and its water-soluble extracts or by desiccated pig's stomach,—and the general view, although there are still great differences of opinion as to the means of so doing, that these degenerative nerve changes can also be prevented and relieved, if present, by dietetic means, support the idea of a nutritional basis being involved.

If, in addition, it is possible by dietetic means to produce and prevent experimentally comparable lesions in the spinal cords and peripheral nerves of animals, involving demyelination of conducting nerves in the absence of inflammatory reaction and neuroglial overgrowth, it will be agreed that such an experimental basis may afford a means of adding valuable knowledge to the metabolic processes which underlie the disorder.

I wish, therefore, to give a bird's-eye view of evidence which demonstrates not only that the spinal cord is within the pale of nutritional influences, but also that the so-called toxic degeneration of the nervous system can be produced by certain ordinary foodstuffs and can be prevented by specific food ingredients; that, in other words, there are neurotoxic agents in food which can only act and hasten demyelinative changes in nerves in the absence from the diet and from the body of certain essential protective factors in food.

My attention was first attracted to this subject about ten years ago when I noticed that some of my experimental dogs in which I was studying the cause of rickets, developed severe inco-ordination of movement and other symptoms of nervous disorder. After having decided that this condition was independent of rickets, I examined their nervous systems and found extensive myelin degeneration in certain parts of the spinal cord [1]. It became evident in course of time that there were two properties of the diet which produced these degenerative changes; (1) it contained much cereal, and (2) it was deficient in fat-soluble vitamins.

Cereal content of diet.—Whereas the nervous changes were evident when white flour formed the cereal factor of the food, they were increased when wheat germ or embryo was added. Since the behaviour of the dogs and the nerve degeneration in the cord reminded me of the clinical condition known as convulsive ergotism in man, it seemed possible that the wheat embryo which increased the morbid changes was ergotized, i.e. invaded by the mycelium, *Claviceps purpurea.* Microscopic examination did not support this possibility, but my attention having been drawn to ergotism, I proceeded to add ergot of rye to the diets and found that this increased the nerve degeneration. Rye germ not infected by the ergot mycelium also increased the cord changes. In fact, it became clear that all cereals tested (with one exception) under these particular experimental conditions, allowed demyelination of conducting nerves in the cord to develop, and that cereal embryo and especially ergotized rye germ made the condition worse. I assumed that cereal and especially cereal embryo and ergot contained a neurotoxin. The exception among cereals was yellow maize for a reason which will be obvious later. When yellow maize was eaten no degeneration was produced even when additional ergot was eaten. White maize, on the other hand, allowed these changes to develop [2].

Vitamin A and carotene as the protective factor.—It has been mentioned above that the cord changes only occurred when the diets were deficient in fat-soluble vitamins, and it became necessary to see which vitamin was capable of exerting this protective influence. At first this was a matter of some difficulty, as the earlier work was done before a clear differentiation between vitamins A and D had been made. With the preparation of pure vitamin D it was possible to add this singly to the diets, and it was then evident that this particular substance was not the protective factor. It was indeed found that ergot itself contained vitamin D, and it was unlikely that a substance which made the degenerative changes worse should contain a protective vitamin in any quantity. Thus while ergot prevented rickets in these young animals, it made the spinal cord degeneration more severe.

When attention was now turned to vitamin A, it soon became evident that this was the essential protective factor, for any source of this vitamin prevented the nerve degeneration. Thus butter, egg-yolk, mammalian liver or liver oil had a protective action. Green vegetables and carrots also had the same protective influence, and this led to the idea that carotene, in this as in other biological properties, acted like vitamin A. This was found to be the case, for the addition of 2 to 3 mgm. of carotene to the diet daily prevented the myelin degeneration even when ergot was present in the diet.

It is impossible here to discuss these experimental results or their significance in any detail, but reference may be made to a few more outstanding points.

(*a*) Of the two dietetic factors which form the basis of these results—a neurotoxic influence associated with cereals, and a protective fat-soluble vitamin—the latter is the more important. In my experience the neurotoxic element is ineffective in the presence of the protective factor. On the other hand, even in the absence of cereal, I have produced similar results in young dogs by feeding them on synthetic diets of pure protein, fat and carbohydrate, such as are given in rat experiments, when the vitamin A and carotene have been deficient. Zimmermann [3] has produced similar results in rats by giving them cereal-free vitamin-A-deficient diets.

(*b*) When cereal is replaced by potatoes, even when the diet is deficient in vitamin A, it is much more difficult to produce nerve lesions, and often the animals remain normal.

(*c*) The reason why yellow maize does not produce nerve degeneration is because it contains carotene as its pigment. White maize, not containing carotene, allows these changes to develop.

(*d*) Although the nerve degeneration changes described are not prevented by adding calcium salts to the diet, it seems probable that a great deficiency of calcium in the diet makes such changes worse. A diet containing only a small quantity of milk, or separated milk, and rich in cereals brings about abundant nerve degeneration, and since additional calcium in the form of calcium carbonate reduces this in amount, it is probably the result of a calcium deficiency. These animals develop very soft bones containing but little calcium salts, and quickly become paralysed. It is probably this condition which accounts for Stockman's recent results, in which he obtained demyelination changes in the cord of animals receiving diets rich in maize and other cereals, and deficient in calcium-containing foods.

Distribution of central nervous lesions.—In the absence of vitamin A and carotene, the nerve degenerative changes are especially seen in the spino-cerebellar tracts, the posterior tracts, and the anterior lateral columns. It is probable that the fibres principally affected are ascending, and that the crossed pyramidal tract usually escapes. The distribution of the degenerating fibres varies at different levels of the cord [2].

Above the medulla, spino-cerebellar fibres entering the cerebellum *via* both the inferior and the superior peduncles show degenerative changes. Other tracts affected include the fillet and the posterior longitudinal bundle.

Above the mid-brain the number of fibres showing myelin degeneration is greatly reduced, but it is quite clear from the behaviour of the animals that the higher parts of the brain do not escape the harmful effect of these diets. These animals when affected are stupid and incapable of fixing their attention on any definite object. In some cases, at least, the cerebral nerve-cells suffer degenerative changes, but this part of the nervous system has not yet been properly examined. Other nerve-cells, such as Clarke's column cells, Purkinje's cells, cells of the dentate nucleus, and, to a less extent, the anterior horn cells, are all apt to show chromatolysis, shrinking, excentric nuclei, and many glial cells in the immediate vicinity.

Changes in the peripheral nerves.—A more recent development of this experimental work is the discovery that the peripheral nerves are also involved in similar degenerative changes [4]. It would indeed appear that most afferent nerves suffer myelin degeneration. Thus the vestibular and cochlear divisions of the eighth, the optic nerve, the ophthalmic division of the fifth and the sciatic nerves when stained by the Marchi or Scharlach method show characteristic degeneration. At least in the early stages, and before paralysis develops, the efferent nerves seem to escape. This fact becomes evident on examination of the anterior and posterior roots of the cord. As a general rule, the anterior roots of animals brought up on these vitamin A-deficient diets are free from degenerating fibres while the corresponding posterior roots are greatly affected.

These changes in the afferent nerves are probably of great significance, especially in relation to the increased susceptibility of epithelial surfaces to infection which develops when diets are deficient in vitamin A [4].

Have the foregoing facts any relation to subacute combined degeneration of the cord ?—Here again, as has happened on several occasions in recent years, we see a series of morbid lesions produced experimentally in animals by certain defined conditions showing a close similarity to a well-recognized disease found in man, and it is our duty to see whether the ætiology of the animal and human diseases respectively bear any relation to one another.

It can be said at once that, if there is any such relationship between the animal experiments just described and subacute combined degeneration of the cord in man, it cannot be as direct, as appears to be the case between these experimental results and such nutritional diseases as convulsive ergotism, pellagra and lathyrism. In all the latter there is strong evidence that a vitamin-A deficiency, associated with excessive intake of some foods containing neurotoxic elements, accounts in large part for the nerve lesions. This suggestion does not, of course, preclude the possibility of other factors being also involved. In subacute combined degeneration, however, the complete absence of vitamin A from the food or from the body is unlikely, and since the experimental lesions only develop in animals when there is little or no vitamin A stored in the body, this single explanation cannot alone account for the clinical condition.

Because a substance such as vitamin A is present in the food, it does not mean that it is effective. It may not be stored in the body, or it may not be transferable to some seat of action, or its effectiveness may depend on the presence of a correct amount of some other chemical agent. It can be stated definitely, however, that not only does subacute combined degeneration develop when there is vitamin A in the diet, but also that this substance is stored in the liver in this disease, so that, if it is ineffective, it is for some other reason.

It is, however, only with much hesitation that I advance an argument of this type, because we have in recent times become so accustomed to see the specific effects of deficiency and excess of certain substances of physiological importance that it is difficult to imagine conditions where they are ineffective when present or, when absent or deficient, that processes which they control can be normal. Such occasions do arise, however, as, for instance, in diabetes mellitus, when the pancreas contains insulin which is relatively ineffective. We know also from the work of Houssay that whether insulin is active or not depends on the condition of the pituitary body, and the loss of the pituitary gland greatly increases the susceptibility of the animal to insulin. Thus removal of the pancreas does not produce diabetes in an animal deprived of its pituitary body.

Another instance of a similar nature is seen in the case of thyroxine, a substance which in minute quantities raises the basal metabolic rate of normal animals. In patients with nephrosis, however, it is difficult to raise their metabolism by this means. Thus there are analogous cases which show that the effectiveness of specific active principles can be modified by other metabolic changes.

Now it happens that in subacute combined degeneration, whatever the metabolic basis at fault, there is good evidence which shows that chemical elements quite sufficient in amount in the normal body to carry out their function, are insufficient to work effectively in controlling the nervous tissues. Thus it is generally accepted that the amount of liver or liver extract sufficient to improve the blood condition in pernicious anæmia to one approaching normality, say with a hæmoglobin reading of 80%, is insufficient to prevent the onset of subacute combined degeneration or to improve it, if it has already developed. Some claim, however, that, if the hæmoglobin content of these patients be increased to 100% by giving huge amounts of liver extract, the nerve disorder is prevented, or improved if present. Thus, even if we accept the view that the chemical agent responsible for the blood improvement and the nervous system control is the same, it is obvious that in these associated diseases very much larger quantities of this substance are necessary for the protection of the nerve metabolism than for improvement of the blood condition—a quantity out of all proportion larger than that effective in the normal man.

Or take the iron treatment as recommended by Sargant [6]. The body is loaded with iron in pernicious anæmia at a time when the blood condition is bad and subacute combined degeneration is developing rapidly. If Sargant's deduction from his results is correct—that excessive iron therapy in the form of 120 to 150 grains of Blaud's pill daily—greatly and specifically improves the nerve disorder, this can only mean that the stores of iron already present are ineffective. Whether we assume, therefore, that excessive liver principle or excessive iron acts in a preventive or curative way in subacute combined degeneration, it is clear that ordinary or normal quantities of these substances are ineffective in preventing or curing the nerve condition. Now the present experimental work indicates that the cord-changes are not controlled by the water-soluble fraction of liver which cures the blood condition, but that they are controlled by a fat-soluble fraction of liver, namely, vitamin A. I have found in animal experiments that water-soluble fractions of liver which are curative of the blood condition in pernicious anæmia do not prevent central and peripheral degeneration of medullated nerve-fibres. The fat-soluble fraction of liver, on the other hand, has this effect. Incidentally it may be added that desiccated pig's stomach also does not prevent demyelination of nerve-fibres in these experimental animals.

Thus, both from the positive and the negative side, the experimental evidence on animals supports the view that myelin degeneration of medullated nerves in subacute combined degeneration is dependent on the ineffective action of a fat-soluble fraction of the liver and not on the water-soluble factor of liver or on the enzyme of desiccated stomach. Thus, on the analogy of the excessive liver extract and iron therapy combined with the animal experimental results, it may well be that vitamin A, although present in the liver of these patients, cannot, for some unknown reason, carry out its ordinary work of controlling nerve function and structure.

It will be asked, however, whether there is any clinical evidence that vitamin A or carotene given in excessive amounts, as in the case of liver extracts or iron, effects beneficially subacute combined degeneration, or even whether their influence is of any significance in this disease. There is certainly no good evidence of this at present. Cases of subacute combined degeneration under my care have never been given a diet whose only good quality was its high vitamin A content. I have always given them whole liver in large quantities together with other dietetic substances of high biological value, and although my experience is small, my impression is that such diets have proved effective both in staving off the nerve derangement and improving the condition of those who have developed the disorder. The diet I give, besides containing ½ lb. mammalian liver daily, includes 2 pints of milk, one or two eggs or their yolk, abundant vegetables, especially green vegetables, and cod-liver oil, ½ ounce. It is obvious that the beneficial effect on subacute combined degeneration of such a diet cannot be ascribed solely to its vitamin A and carotene content. Although I cannot give any direct clinical evidence of the suggestion, based on the animal experiments, that vitamin A is an ætiological factor of importance in this disease, I have never felt justified in the treatment of these patients to disregard the experimental evidence and its possible significance. Nor do I consider that it is right, on the basis of our present knowledge, to give such patients liver extracts without taking into account the rest of the diet. Indeed, it seems to me probable that the amount and severity of subacute combined degeneration that is described as occurring nowadays may be due to the giving of liver extracts only, which improve the blood condition and lengthen the life of these patients without preventing the nerve degeneration.

Before leaving this aspect of the subject, it may be well to mention that in the case of the only two post-mortem examinations of pernicious anæmia with subacute combined degeneration of the cord that I have personally seen during the last few years, the cause of death was pyelonephritis. The possible significance of this lies in the fact that pyelonephritis is a common occurrence in vitamin-A-deficient animals. The livers of both of these patients contained vitamin A, so that if vitamin A is of any importance in the condition under discussion, it must be concluded that it was ineffective both as regards the condition of the kidneys and the nervous system, either because it could not be mobilized or because it could not be used by the respective cells.

In conclusion, let me say a few words as to what would be expected to result from dietetic treatment in subacute combined degeneration, especially in established cases. Dr. Carmichael has emphasized in his recent work that the peripheral nervous system is largely involved in this disease and that in curative results that are seen nowadays it is primarily changes in the peripheral nervous system that account for the improvement. Similar results have been described by Baker, Bordley and Longcope [5] in a series of cases of subacute combined degeneration.

In my experimental animals also, as mentioned above, the afferent peripheral nerves as well as those of the central nervous system show degenerative changes. Whereas certain early changes in the peripheral nerves, such as those found in the ophthalmic division of the trigeminal nerve associated with early xerophthalmia, heal up quickly on giving vitamin A, more severe degenerative changes may take months before the demyelination clears up and the nerve function is completely restored. I mention this fact because, as pointed out by Baker, Bordley and Longcope, many clinicians seem to expect curative results too quickly from the treatment of subacute combined degeneration of the cord. Where fibres in whole areas of the cord have disappeared, it would not be expected that any form of therapy would restore this function. On the other hand, it would be definitely expected that peripheral nerve lesions would clear up. Even in this case, however, if these are severe, such improvement would not be expected until after months of treatment. Baker, Bordley and Longcope say that nine months may be necessary. If continuous dietetic treatment cures, as it is now known to cure, the peripheral nerve lesion, it is probably safe to assume that the cord degenerative changes are stopped. Thus, even in severe cases of subacute combined degeneration, beneficial effects may be expected from this type of treatment, due both to the recovery of peripheral nerves and to the prevention of further central degenerative changes.

To sum up the present position in the light of the experimental and clinical work referred to above, it would appear that—

(1) The nervous system is greally influenced by nutritional factors, since it is possible to produce in young animals demyelination changes in medullated nerve-fibres of both the central and peripheral systems, which are similar to—probably in many respects identical with—those of convulsive ergotism, pellagra, lathyrism and subacute combined degeneration, i.e. the well-known toxic degenerations of the nervous system. In these experiments absence of vitamin A and carotene from the diet is the chief factor, but the condition may be hastened by adding cereals or cereal products such as embryo or ergot.

(2) Whereas these results probably account largely for the nerve lesions in convulsive ergotism, pellagra, and lathyrism, they cannot alone explain the nerve lesions of subacute combined degeneration, because in this disease the body contains vitamin A.

(3) If the animal experiments mean anything in relation to subacute combined degeneration—and the close similarity of the peculiar lesions suggest that they must do so—it can only be assumed that, for some unknown reason, vitamin A cannot be mobilized or cannot carry out its normal function in ordinary quantities in this disease. Reasons have been given to show that some other essential chemical substances in the body are also relatively ineffective in this disease.

There is clearly a gap to be bridged between the experimental and clinical knowledge. What is wanted is knowledge as to those conditions which prevent vitamin A from acting in the body in ordinary quantities. I know of no such conditions as yet. Possibly the associated condition, in subacute combined degeneration of achylia gastrica, may afford the clue to the missing link. However, I have never yet seen this condition in my experimental animals.

In the meantime it seems to me that experimental work of this type may ultimately lead to the solution of the clinical problem, and that the results ought to be regarded at least as of possible significance. Such patients should therefore be given not only the water-soluble fraction of liver known to cure the blood condition, but also large quantities of vitamin A, either in the form of substantial quantities of whole liver or its fat-soluble fraction, such as mammalian or fish oil, as well as milk, eggs and green vegetables.

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